Enfermedades Infecciosas y Microbiología Clínica 39 (2021) 369–371

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Editorial

Women, men, and HIV infection: One virus, two epidemics

Mujeres, hombres e infección por VIH. Un virus, dos epidemias

Discussing the differences between men and women is certainly polemical. Although we can adhere to biology as the most reliable science for making distinctions between the sexes, deeper examination of the psychological, sexual, cultural, or role-based spheres is sure to spark debate. These issues show so much overlap between the sexes that we must turn to statistics and clinical epidemiology to understand and assess differences. Clearly, we do not have to make forced or excessive distinctions among genders in the area of infection with HIV. The pathogeny, clinical features, diagnosis, and treatment are similar for men and women. There are, however, distinctive differentiating aspects worth mentioning. The specific impact of HIV infection on women merits attention and analysis.

Women represent 50% of the global population living with HIV. Heterosexual relationships are the most common risk factor among women, far surpassing transmission through injected drug use. Factors that encourage HIV transmission are sexually transmitted infections (STIs), high viral load (VL), and unprotected sex.[1] More specifically, the prevalence of HIV infection in transgender women is estimated to be extremely high, affecting as much as one fifth of this population.[2]

At the start of the epidemic, various studies showed higher mortality and progression of HIV in women than in men. These data may perhaps be explained, however, by various confounding factors. It is probable that less access to antiretroviral treatment (ART) and insufficient care for the illness is more decisive than a more aggressive course of HIV in women.[3–6] Delayed diagnosis is also more common in women than in men; one third of women either show symptoms of AIDS or develop it in the first 12 months after diagnosis. Decrease in AIDS-associated mortality was initially less intense in women than in men,[7] although survival rates three years after diagnosis are currently similar.

From a virological perspective, a now classic study of 650 injected drug users (IDUs) identified different measurements of VL between men and women, with women showing approximately half the VL after adjusting for number of CD4 lymphocytes. In this study, given equal VL and CD4 count, women had a 1.6 times higher risk of progressing to AIDS than men. Although initial HIV-1 RNA level is somewhat lower in women than in men, progression rates of the disease seem similar.[8,9] A lower level of VL in women than in men could, on the other hand, contribute to a lower rate of transmission from women to men. Higher VL in men, in contrast, strengthens likelihood of a higher transmission rate in receptive vaginal sex (among other factors).

Regarding clinical manifestations, with a few exceptions, opportunistic infection rates do not differ.[10] Kaposi's sarcoma (KS) continues to be higher in men. Women with KS tend to present more advanced and extensive diseases, possibly related to delay in diagnosis.[11] Various studies of cohorts have reported higher incidence of esophageal candidiasis, bacterial infections, and herpes simplex virus (HSV) infections in women.[6,12] For many women, gynecologic complaints are the initial manifestation of infection with HIV. Although these problems occur in women who are not infected with HIV, they are more frequent and more serious in women with HIV. Examples are Candida vaginitis,[13] bacterial vagininosis,[14] abnormal cervical cytology, pelvic inflammatory disease, genital ulcer disease (for example, HSV, chancroid, syphilis), and menstrual disorders. The highest risk of cervical disease in women with HIV is related to degree of immunosuppression (CD4 cell count), co-infection with high-risk genotypes of the human papilloma virus (HPV),[15] age,[16] and cutaneous anergy.[17] Women with HIV are more likely to present multifocal cervical disease and to progress more rapidly to uterine cervix cancer.

As to ART, efficacy of ART seems generally comparable in men and women in its virological, immunological, and clinical results, after controlling for possible confounding factors,[18] although some clinical trials showed worse results for women with atazanavir than with efavirenz.[19] It is important to highlight that women are often underrepresented in randomized clinical trials of HIV-1 drugs, prophylactic vaccines, and curative strategies.[20] Although immuno-virological efficacy is the same in men and women,[18] the dropout rate is higher in women, due mainly to social or economic problems.[21,22] On the positive side, the prevention of mother-to-child transmission has allowed women access to treatment in many countries and has clearly contributed to improving survival, especially in Africa.

The desire for fertility and the best method for birth control should be addressed for all women of reproductive age. Pregnancy tests should be performed before starting ART, since pregnancy affects choice of ART and use of other medications that can be prescribed for infection with HIV. Choice of antiretroviral regimens for women of reproductive age merit special consideration. Data from the "Tsepamo cohort" raised concerns about the slight potential risk of neural tube defects with exposure to dolutegravir

DOI of original article: https://doi.org/10.1016/j.eimc.2020.05.021

https://doi.org/10.1016/j.eimc.2021.06.005

at time of conception.[23] Although bictegravir and tenofovir alafenamide are commonly used in the general population, data on their safety and dosage during pregnancy are limited. Persons planning actively to conceive and to begin ART usually avoid regimens with dolutegravir, bictegravir, and tenofovir alafenamide and are instead usually prescribed raltegravir, darunavir, or atazanavir boosted with ritonavir and tenofovir disoproxil fumarate.

In this journal issue, Dr. Muñoz Hornero et al.[24] tackle the question of whether substantial epidemiological, evolutionary, and mortality-related differences exist between men and women infected with HIV. To determine this, they analyze the best cohort available in Spain for examining this question: the CoRIS cohort for the time period 2004–2014, when ART is fully established. This period is stratified into three periods of 3.5 years each for convenience. According to their data, the incidence rate ratio of men to women is approximately 5. For each 100 new HIV diagnoses, 83 are men and 17 are women. Further, this imbalance increases over time; in the last period, only one of every 10 new cases is a woman.

Women are diagnosed late (late presentation) and poorly (high number of AIDS-defining events). It is true that more diagnostic tests for HIV are performed on men who have sex with men (MSM) than on women or immigrants.[25] Women immigrants are currently the group most castigated by HIV, constituting nearly 50% of women living with HIV (WLHIV). In the stratified analysis the authors propose, immigrant women infected with HIV are younger than their Spanish counterparts and less likely to have hepatitis C virus (HCV) or be IDUs, but they have higher rates of hepatitis B (HBV) and syphilis infection.

The cohort's characteristics change over time. Over the years, fewer IDUs enter the cohort, as well as fewer women co-infected with HCV, more foreigners, older women (especially Spanish women), and fewer women at the stage of AIDS. Despite these data, 15% of women still present stage C on diagnosis in the third period of the cohort, as opposed to 8% of men, and nearly 30% present < 200 CD4 lymphocytes/mm^3, as opposed to 17% of men. Although syphilis occurs 4 times more frequently in men than in women, diagnosis and treatment are crucial in women to avoid congenital syphilis.

Mortality does not differ between men (3.4%) and women (4.1%) in the study over time. Crude mortality rate varies with the period: fewer women than men die in period 1 and more women than men in period 3. Adjusting for diverse variables that impact mortality (such as age, education level, immunosuppression, co-infection, and stage of AIDS), however, gender is not independently constituted as an explanatory variable. It is not so much sex, but rather when and how women arrive at diagnosis and treatment of HIV, as well as other socio-epidemiological factors, that lead to greater morbimortality. If we also consider that women's life expectancy in the general population is greater than men's, the fact that women with HIV die at a rate similar to men suggests that certain associated factors castigate women in particular, affecting them more than men compared to women not infected with HIV.

It must be stressed that the absolute number of persons who have died and the number of persons at risk differ in each period. The data on survival provided in this study are difficult to compare, since the monitoring time varies among the three periods and the y-axis varies from figure to figure. Analyzing mortality by period in short periods of time makes it unlikely that statistically significant differences will occur with such a small number of deaths. Other cohorts with more subjects and deaths or with longer monitoring show lower mortality in women[26] or do not detect clear differences according to sex.[27]

The HIV infection itself, and then, neoplasia, are the most frequent causes of death and do not show statistically significant differences between sexes. The news is not all bad for women. First, it is striking to note that not one woman in all three periods died of cardiovascular causes. This makes sense if we understand that this cohort includes a population recently diagnosed with HIV infection and that 75% of the cohort is under 45 years of age on entry. Second—and these are favorable data—overall mortality decreases over the periods, from 265/3480 (7.6%) in the first period to 121/3408 (3.6%) in the second, and 66/3561(1.9%) in the third.

The study by Muñoz Hornero et al. is very useful and significant. It gives us not a snapshot but a video of how the HIV epidemic is evolving in Spain. Admittedly, although we are facing the same virus (HIV), we see two epidemics: one that affects men and one that affects women. Whereas mortality and its causes do not seem very different, there are distinctive elements for women that help us to focus specific attention on this group. As doctors, we must be especially sensitive to women, particularly immigrants and those with low education levels, to attend not only to their medical needs but also to their social, cultural, reproductive, and family necessities.

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